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ANNUAL 1 Jun 93 TO 31 May 94

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TOXIC SUBSTANCES ON THE LUNGS

5. FUNDING NUMBERS

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6. AUTHOR(S)

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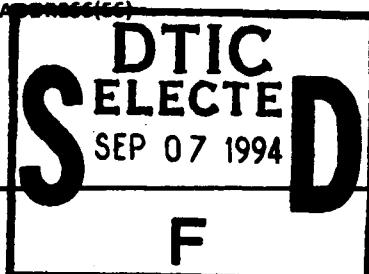
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13. ABSTRACT (Maximum 200 words)

Allison and Brian will continue to work on the chronic jet fuel exposure research project. However, Allison will also participate in our magnetic resonance imaging (MRI) project. We are attempting to develop a portable MRI system for deployment on either the Space Shuttle or Space Station. In addition, we are studying the possibility of using MRI in our toxicology experiments to determine changes in blood flow and organ perfusion after exposure to environmental toxins. Both Allison and Brian are intelligent students and I expect them to maintain their high level of performance in their coursework.

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SECOND YEAR SUMMARY FOR AASERT GRANT

ENTITLED

**RESEARCH TRAINING OF THE EFFECTS OF TOXIC SUBSTANCES
ON THE LUNGS**

Mark L. Witten, Ph.D. Principal Investigator

Department of Pediatrics

Arizona Health Sciences Center

Tucson, Arizona

94-28979



(6P)

Submitted to-

**Life and Environmental Sciences Directorate
U.S. Air Force Office of Scientific Research
Bolling Air Force Base, DC 20332-6448**

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Overall Progress of the Grant

Allison M. Hays and Brian Tollinger are the students supported by the AASERT Training grant. Allison has been accepted into the graduate program in the Department of Exercise and Sports Sciences at the University of Arizona. Brian has worked in my laboratory for the past two years. Brian is a graduate student in the College of Pharmacy at the University of Arizona. Both Brian and Allison are doing well in their graduate programs. In addition, both students presented abstracts concerning the effects of chronic jet fuel exposure on lung function at the Experimental Biology '94 meeting in Anaheim, California (please see enclosed abstracts). Both Allison and Brian are spending the summer months converting their abstracts into manuscripts that will be submitted for publication.

Plans for Year 3 of the Grant

Allison and Brian will continue to work on the chronic jet fuel exposure research project. However, Allison will also participate in our magnetic resonance imaging (MRI) project. We are attempting to develop a portable MRI system for deployment on either the Space Shuttle or Space Station. In addition, we are studying the possibility of using MRI in our toxicology experiments to determine changes in blood flow and organ perfusion after exposure to environmental toxins. Both Allison and Brian are intelligent students and I expect them to maintain their high level of performance in their coursework.

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ALA-P-NITROANILIDE, A SUBSTRATE CLEAVAGE PRODUCT
OF NEUTRAL ENDOPEPTIDASE, LEVELS ARE INCREASED
AFTER JET FUEL EXPOSURE IN RATS. B.J. Tollinger, A.M. Hays,
R.C. Lantz, P.A. Rittenhouse, and M.L. Witten, Steele Memorial
Children's Research Center and Center for Toxicology, Arizona
College of Medicine, Tucson, AZ and Boston University School of
Medicine, Boston, MA.

Neutral endopeptidase, found in lung epithelial cells, has many roles such as modulation of smooth muscle contraction, mucus secretion, and cell growth. Our previous research has demonstrated that increasing jet fuel (JP-8) exposure concentrations causes a proportional decrease in broncho-alveolar lavage concentrations (BAL) of substance P after a 28 day exposure period with the following groups: control (C), low dose JP-8 (LDJ), and high dose (HDJ). We determined whether increasing jet fuel exposures caused a progressive increase in BAL ala-p-Nitro-anilide levels as determined by high pressure liquid chromatography. The ala-p-Nitro-anilide levels (millimoles/ml BAL) were the following: C (N=7) 0.85 (0.15), LDJ (N=6) 1.33 (0.58), and HDJ (N=7) 3.22 (0.73). We conclude that chronic inhalation exposure to jet fuel causes progressive increases in lung neutral endopeptidase which in turn may be responsible for the decrease in lung substance P levels.

Supported by AASERT/AFOSR 91-0199.

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Mark L. Witten, Ph.D.

Member's Name (Print or type)
Mark L. Witten, Ph.D.

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Dept. of Pediatrics
Arizona Health Sci. Center
1501 N. Campbell Avenue
Tucson, AZ 85724

Phone: (602) 626-6572

Fax: (602) 626-3636

**CHANGES IN LUNG PERMEABILITY AFTER CHRONIC
EXPOSURE TO JP-8 JET FUEL. A.M. Hays, B.J. Tollinger, J.P.
Tinajero, R.F. Robledo, R.C. Lantz, M.L. Witten, Steele
Memorial Children's Research Center & Center for Toxicology.
University of Arizona, Tucson, Arizona. 85724.**

We evaluated the effects of JP-8 jet fuel exposure on lung epithelial permeability in male Fischer 344 rats. Lung injury was measured by alveolar clearance of technetium-labeled diethylenetriamine pentaacetate ($^{99m}\text{TcDTPA}$, MW = 492d, physical $T_{1/2} = 6.02$ h). The % clearance of $^{99m}\text{TcDTPA}$ was calculated and recorded as k. A seven day, 28 day, and 56 day protocol for low dose JP-8 (500 mg/m³/hr) and high dose JP-8 (800-1100 mg/m³/hr) and sham exposed groups was used. The baseline control group (n=21) had a k of 1.66. The 56 day low dose exposed group (n=11) had a k of 1.09 while the 56 day high dose exposed group (n=10) had a significantly higher ($p < 0.05$) k of 2.25. There appears to be an adaptive process after chronic exposure to JP-8 jet fuel that may involve increased fibrosis of the lungs or repair to the alveolar-capillary barrier. Supported by DOD AASERT & AFOSR 91-0199.

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Mark L. Witten, Ph.D.

Member's Name (Print or Type): Mark L. Witten, Ph.D.

Member's Signature Mark L. Witten (602) 626-2610 626-3636

Member's Telephone (602) 626-2610 626-3636

FAX (602) 626-3636

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selecting Mode of Presentation, Block, and
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